YEARBOOK OF PHYSICAL ANTHROPOLOGY 40:1–24 (1997)

# Environmental Change and Cardiovascular Disease: A New Complexity

TESSA M. POLLARD

*Department of Anthropology, University of Durham, Durham, DH1 3HN United Kingdom*

*KEY WORDS* modernisation; undernutrition; infection; sex; estrogen; diet; stress

*ABSTRACT* Cardiovascular disease has for many years been considered a lifestyle disease, caused by westernisation or modernisation. The most important lifestyle risk factors are thought to be diet (particularly high levels of saturated fats and excess salt), lack of physical activity, obesity, psychosocial stress and smoking, all of which are identified with modern living in industrial societies. This paradigm goes some way towards explaining observed inter- and intrapopulation variation in the prevalence of cardiovascular disease, but does not explain all such variation. It is important that physical anthropologists start considering new hypotheses concerning quite different risk factors. It has been suggested that undernutrition in fetal and early infant life may program physiological systems such that later exposure to lifestyle risk factors are particularly dangerous. A quite different theory links infection with certain bacteria, and perhaps viruses, to increased risk of cardiovascular disease. Both these proposed risk factors are much more prevalent in developing countries and poorer populations, although they may only become important when well-known risk factors are introduced too. The possible protective role of estrogen in women and the light which anthropologists' work on ovarian function throws on its potential for impact in different populations are also discussed. Future attempts to explain variation in cardiovascular disease risk will require a new complexity of approach. It will be particularly interesting to consider the interaction between maternal and infant undernutrition, infectious disease load, hormonal changes and cardiovascular disease in modernising populations. Anthropologists are well placed to undertake such investigations. Yrbk Phys Anthropol 40:1–24, 1997.



Historical and geographical trends indicate a clear link between the lifestyle typical of people in urbanised industrial countries and the prevalence of cardiovascular diseases (CVDs). In the 20th century CVDs have become, with cancer, one of the two most important causes of death in these countries. Many of the concurrent changes in lifestyle which were at least partly responsible for the increase in the rates of these degenerative diseases have been identified, including changes in diet and physical activity levels. Confirmation of the risks associated with the modern industrial lifestyle comes from observations that CVDs are a relatively unimportant cause of mortality in parts of the world where similar changes have not occurred, but that in populations in developing countries death rates from CVDs are rising (Pearson et al., 1993). Cardiovascular disease has thus become known as a western disease, or a disease of modernisation (Trowell and Burkitt, 1981; McGarvey et al., 1989).

However, within this broad association between the industrial lifestyle and CVD there is much variation (Kunitz, 1994). There is a wide range in CVD mortality rates and the comparative prevalence of different CVDs (heart disease, stroke and hypertension) in industrial and developing countries, as well as in elevation of physiological precursors to disease, such as obesity, blood pressure, and serum total and low-density-lipoprotein cholesterol levels. Some modernising populations have shown very high rates of CVD and others have not (Kunitz, 1990). It is important to look beyond the simple equation of modern industrial living with CVD to explain these findings. We need to disentangle the individual components of the modern lifestyle, since they do not always occur together. However, even when disaggregated they do not appear to be able to explain all variation in CVD prevalence. For example, Dwyer and Hetzel (1980) found that changes in diet and smoking habits go only part of the way towards explaining recent declines in coronary heart disease mortality in Australia, the United States and England. It is important, then, to consider new hypotheses and findings which have identified quite different environmental risk factors.

The aim of this review is first to summarise briefly our current state of knowledge with respect to well established environmental risk factors for CVD, that is, those that are very well known, although not necessarily well understood. Here I highlight recent findings. Next, new and very different ideas about environmental risk factors for CVD are discussed, and their potential to explain some of the variation in CVD profiles in industrial and developing countries, and particularly in modernising populations, is considered. (I use the term "modernisation" because it is widely understood and difficult to replace. It is not meant to connote simple, generalised or progressive change.) These new hypotheses have been stimulated partly by the failure of the well-known risk factors to explain all variation in CVD prevalence. I focus on the effects of early growth, infection and estrogen on risk of cardiovascular disease, and highlight the potential interactions between anthropological and epidemiological work in these areas.

## PATHOGENESIS OF CARDIOVASCULAR DISEASES

The term CVD is used here to include coronary heart disease, stroke, hypertension and hypertensive heart disease. These are the most important causes of CVD morbidity and mortality, and all are usually found in conjunction with atherosclerosis. The earliest manifestations of atherosclerosis are fatty streaks in the artery walls, seen in most children in industrial societies, which may progress to become fibro-lipid plaques from the third decade of life onwards (Fuster et al., 1992a). These atherosclerotic plaques narrow the lumen of the artery, and can trigger platelet aggregation, causing thrombosis and resulting in complete obstruction of the artery (Fuster et al., 1992a, 1992b). When coronary arteries are affected in this way the loss of blood supply to the heart results in coronary or ischemic heart disease. Strokes are often precipitated by the same mechanism in the brain (atherothrombotic stroke), although strokes can also occur due to bleeding in the brain, usually associated with hypertension (hemorrhagic strokes). Hypertension is often found in association with atherosclerosis and probably contributes to the atherosclerotic process by causing damage to the arterial wall, which precipitates local atherosclerosis (Chobanian and Alexander, 1996). Hypertension appears primarily to be caused by increased peripheral vascular resistance as a result of widespread constriction of the arterioles and small arteries (Julian and Cowan, 1992). Hypertensive heart disease results as the heart is forced to work harder and develops left ventricular hypertrophy, which may progress to left ventricular failure.

Hyperlipidemia is strongly associated with atherosclerosis. Lipid deposition occurs at an early stage in atherosclerosis (Fuster et al., 1992a) and there is a high incidence of atherosclerotic disease in individuals with elevated plasma lipid levels (Julian and Cowan, 1992). There is increasing epidemiological evidence that high levels of low density lipoprotein (LDL) are more important than total cholesterol levels in increasing risk, whereas high levels of high density lipoprotein (HDL) are protective against ath-

erosclerosis. A high LDL/HDL ratio favours deposition of cholesterol into the arterial wall (Kannel, 1987).

Insulin resistance has largely been considered as a risk factor for diabetes mellitus. However, insulin resistance syndrome or Syndrome X, which describes a complex of pathologies including insulin resistance, hyperinsulinemia, abdominal obesity, and dyslipidemia with high triglyceride and low HDL levels, is associated with hypertension and is a risk factor for other forms of cardiovascular disease (Reaven, 1988; Heller and Heller, 1995; Stern, 1996). There is some debate regarding the mechanisms linking insulin resistance and cardiovascular disease (Fontbonne, 1994; Jarrett, 1994; Reaven and Laws, 1994; Stern, 1994). It has been proposed that hyperinsulinemia may be associated with hypertension because insulin can stimulate sympathetic nervous system activity and thus catecholamine levels, leading to raised blood pressure (Stern, 1996). However, recent studies suggest that insulin does not act as a direct risk factor. Anderson and Mark (1993) draw attention to research showing that insulin has vasodilating properties so that overall it does not, at biological concentrations, increase blood pressure. Anderson and Mark (1993) note suggestions that, conversely, abnormalities in skeletal muscle vascular and sympathetic mechanisms in hypertension may cause insulin resistance. The links between insulin resistance and cardiovascular disease are not yet clarified and are under active investigation.

A raised level of the serum protein fibrinogen has recently been recognised as a predictor of ischemic heart disease. In a meta-analysis of prospective studies (unfortunately almost all conducted only with men) Ernst and Resch (1993) showed that fibrinogen was a risk factor, independent of other known risk factors. One such study was conducted in the United Kingdom by Yarnell et al. (1991), in which fibrinogen levels did not show strong correlations with total cholesterol, blood pressure or body mass index, but did predict ischemic heart disease 3–5 years later. Ernst and Resch (1993) assessed the evidence for a causal relationship and suggest that it is strong, despite the methodological problems caused by the fact that fibrinogen levels are known to be elevated after an acute myocardial infarction or stroke, as part of the acute-phase response to inflammation. Fibrinogen could contribute to atherosclerosis and thrombosis via its effects on endothelial function and platelet aggregation. These findings suggest that in the future it will be important to consider measuring fibrinogen levels in population surveys.

Most recently, it has become clear that nitric oxide is involved in physiological processes associated with CVD, including vasoconstriction, atherosclerosis and thrombosis (Dusting, 1995; Kuo and Schroeder, 1995; Lüscher and Noll, 1995). A link between endothelial nitric oxide production and insulin sensitivity has been suggested (Petrie et al., 1996). In general, higher levels of nitric oxide are considered to protect against cardiovascular disease. Nitric oxide is subject to intensive investigation at present so that much more is likely to be revealed about its role in the near future.

Figure 1 shows a simplified scheme of the pathogenesis of cardiovascular diseases, indicating the links between the best known biological risk factors. In population-based studies, serum lipid levels (particularly LDL and HDL cholesterol levels) and blood pressure are the most commonly measured biological risk factors for cardiovascular disease. Increasingly, serum glucose and insulin levels, and sometimes insulin resistance and fat distribution, have also been assessed.

## WELL-KNOWN LIFESTYLE RISK FACTORS

A brief review of the well-known lifestyle risk factors for CVD is offered, with a focus on recent elaborations and on the ability of these risk factors to explain variation in CVD, especially amongst societies undergoing modernisation. The reader is referred to previous reviews of this area for a more comprehensive treatment of relationships between lifestyle and cardiovascular disease (e.g. Kannel, 1987; Jenkins, 1988; Lloyd, 1994).

### Diet, physical activity and obesity

When human subsistence strategies change from foraging to subsistence farming

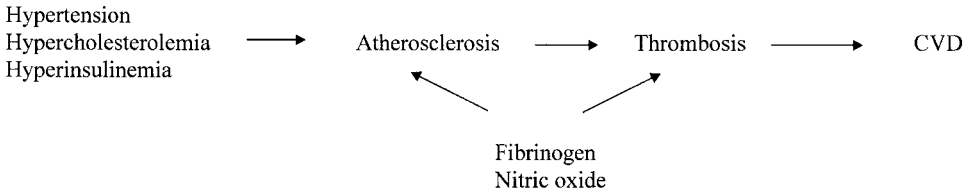


Fig. 1. A simplistic scheme showing the best known physiological pathways leading to cardiovascular disease.

and then to the intensified farming and trade by specialists typical of modern industrial societies, diet changes substantially (Cohen, 1989). The so-called "western diet" is strongly characterised by a high content of refined carbohydrates and fat and usually contains more salt than traditional diets. It is also low in fibre because consumption of fruit and vegetables is generally low compared to that in other societies (Fig. 2). O'Dea (1984) demonstrated the advantages of a traditional diet over the western diet by showing that a temporary reversion to such a diet by a group of Australian Aborigines alleviated abnormalities of lipid and carbohydrate metabolism. In industrialised Asia the diet shares some characteristics with the western diet but tends to be lower in fat (Epstein, 1989).

There is a great deal of evidence linking dietary fat consumption to cardiovascular disease. Total fat intake is an important risk factor and most deleterious is saturated fat, which is mainly derived from animals. Countries which have recently shown major declines in coronary heart disease mortality have also shown declines in animal fat consumption, e.g. the United States, Australia and Canada (Epstein, 1989). In the United States, vegetarians, of which there are an increasing number, have been shown to have less hypertension and lower concentrations of total cholesterol and LDL cholesterol than people eating an omnivorous diet (Melby et al., 1994). Mono-unsaturated and polyunsaturated fats have less consistent relationships with cardiovascular disease (Dimmitt, 1995) and there are no clear trends in vegetable fat consumption in countries in which coronary heart disease mortality rates have declined (Epstein, 1989). Unsaturated fats decrease LDL levels, but it is not clear that they provide protection from cardiovascular disease. For example, lipoproteins are more likely to be deposited in the arteries if they are oxidated and LDL enriched with polyunsaturated fats is more prone to oxidation (Dimmitt, 1995). Dietary antioxidants, which

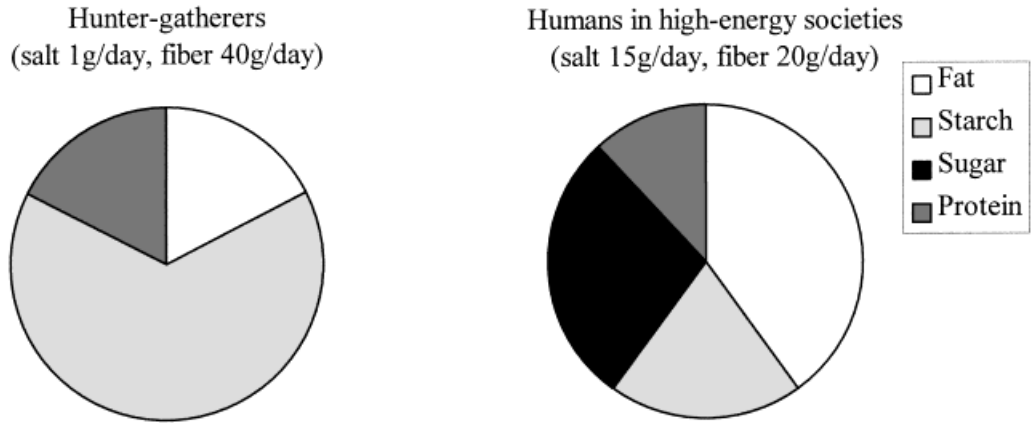


Fig. 2. Approximate percentage of energy from food components, and salt and fiber intake, for people living as hunter-gatherers and in modern industrial societies (adapted from Boyden, 1987).

include vitamins C, E and beta-carotene, probably have a protective role because they help prevent oxidation of LDL (van Poppel et al., 1994; Stampfer and Rimm, 1995). Hydrogenated unsaturated fats, containing trans-fatty acids, increase LDL concentrations (Feldman et al., 1996). The only fats which appear to have clear beneficial effects are fish oils containing omega-3 fatty acids, consumption of which has been shown to reduce blood pressure (Morris et al., 1993). The unusual traditional diet of the Inuit in Greenland contains high levels of omega-3 fatty acids which are thought to protect them from cardiovascular disease, despite the high overall fat content of the diet (Dyerberg, 1989). It is important, therefore, that in considering the effects of environmental change in any one population, changes in the type of fat consumption are understood.

Sodium has long been identified as a risk factor for hypertension and hemorrhagic stroke. Consumption of sodium has been shown to correlate with blood pressure both across and within populations (Elliott et al., 1996). The majority of sodium in modern industrial diets is added during food processing and cooking and current diets in richer countries contain considerably more sodium than most traditional diets (Fig. 2). Sodium is thought to raise blood pressure by causing an increase in extracellular fluid volume. The ratio of sodium to potassium in the diet appears to be particularly important (Meneely and Battarbee, 1976; Preuss et al., 1996). Young et al. (1995) suggest that renal vascular resistance is reduced and glomerular filtration rate is increased by elevation of plasma potassium, both effects which counteract those of sodium on blood pressure. Furthermore, Young et al. (1995) propose mechanisms by which potassium slows the process of atherosclerosis. The human body has efficient mechanisms for conserving sodium and also for eliminating potassium, perhaps because sodium was scarce, and potassium abundant, in the environment in which humans evolved. Boyden (1987) suggests that our current taste for salt can be explained by the fact that it was once adaptive to enjoy salt, because this would contribute to the appetite for meat, promoting consumption of animal protein with its many essential amino acids.

Moderate alcohol consumption is thought to protect against cardiovascular diseases (Marmot, 1984), although Shaper (1995) has recently drawn attention to methodological flaws which may have led to too ready an acceptance of this effect. Excessive alcohol consumption is an important risk factor for cardiovascular disease (James, 1993). Heavy and/or binge drinking is an important element of life in several populations undergoing rapid lifestyle change, including many Australian Aborigine populations (Hunter, 1993; Kunitz, 1994). As a result, alcohol consumption is a particularly prominent and important risk factor for coronary heart disease in Australian Aborigines (Smith et al., 1992; Gracey et al., 1996). Caffeine use may also constitute a risk factor, although its effects have not yet been resolved (Gyntelberg et al., 1995).

It is possible to make generalisations about the differences between traditional and "modern" diets, but there is more variation than is implied by this simple contrast. For example, the US diet has typically contained a much higher proportion of total and saturated fat than that in Japan (total fat provided around 38% of calories in the United States and 9% of calories in Japan in 1960 in the male cohorts included in the Seven Countries Study; Keys et al., 1986), but proportions have since become more similar; approximately 45% and 32% respectively in 1988 (Report of the Cardiovascular Review Group Committee on Medical Aspects of Food Policy, 1994) while the Japanese diet is generally higher in salt (Beilin, 1992), and it is thought that these differences help explain the fact that coronary heart disease is more common than stroke in the United States whilst the opposite is true in Japan (Uemura and Piša, 1988). On a smaller scale, differences in blood pressure and atherogenic lipoprotein profiles between the Bantu populations of two villages only 50 miles apart in Tanzania have been attributed to dietary differences. The fish-eating group showed a lower risk profile than the vegetarian group (Pauletto et al., 1996). Thus variation in diet within traditional

subsistence and industrial environments can be extremely important.

The level of physical activity and thus calorie expenditure forms the other half of the equation determining whether obesity develops. People living in industrial societies are considerably more sedentary than those who must find or farm their own food. As Ulijaszek (1995) notes, office workers are inactive most of the time and even factory workers, who are directly involved in production, usually make use of labour saving devices. Widespread availability of motorised transport also contributes to the reduction in exercise (Ulijaszek, 1996). Davies (1996) suggests that lack of physical activity is the major reason for the low levels of total energy expenditure seen in young children in the United States and United Kingdom and Fontvieille et al. (1993) showed a significant relationship between television viewing and body fatness in 5-year-olds, suggesting that reduced levels of activity in children who watch a lot of television could explain this finding. Thus, those migrating to cities or industrialised countries often experience a decline in their level of physical activity. For instance Greksa et al. (1986) found that aerobic capacity was very low in Samoan men most affected by an urban way of life, largely because of a decrease in activity level. Similarly, Shephard and Rode (1996) report that "acculturation" and assumption of a settled lifestyle has reduced the habitual physical activity of indigenous circumpolar populations. Apart from its role in determining long-term energy balance, there is also evidence that physical activity has independent beneficial effects on lipid profiles, increasing levels of HDL cholesterol (Kannel, 1987), and on coagulation and thrombosis, blood pressure and insulin sensitivity (Report of the Cardiovascular Review Group Committee on Medical Aspects of Food Policy, 1994).

Obesity is probably the best known risk factor for CVDs, although it is not entirely clear whether obesity per se is important, partly because it increases demands on the heart, or whether its role is mediated by its association with other risk factors, such as lipid levels, insulin resistance and blood pressure. Obesity is becoming increasingly widespread in many industrial nations (Seidell, 1995). It is also a common problem in societies undergoing rapid lifestyle change, particularly in Pacific islanders (McGarvey, 1994). Galanis et al. (1995) demonstrated a much greater increase in weight in Samoan men over 10 years from baseline measurements in 1982 than were typical in the United States (a 10.5 kg increase compared to 2.9 kg for US men). It has been suggested that Polynesians may be genetically susceptible to weight gain. However, extreme obesity in these populations does not seem at present to be as strongly associated with mortality as it is in other populations (Baker and Crews, 1986).

It is now well recognised that some patterns of fat deposition bring more risk than others. Specifically, centripetal fat distribution, where fat is carried on the trunk rather than the limbs, is most strongly associated with higher risk of CVDs (Lapidus et al., 1984; Donahoe et al., 1987). Intra-abdominal cells can release fatty acids very rapidly, and it is thought that a high flux in free fatty acids can lead to insulin insensitivity (Garrow, 1993). Galanis et al. (1995) found, in their longitudinal study of Western Samoan men, that change in abdominal obesity over time was inversely correlated with change in HDL cholesterol. Central fat deposition is more common in men than in women and it has been suggested that some of men's greater risk of CVDs stems from this fact.

Together, diet, physical activity and obesity account for a great deal of variation in CVDs. They are a primary focus of public health intervention strategies. However, even together they cannot explain all variation in CVD prevalence.

## Stress

Psychosocial stress is now widely considered to be a risk factor for CVD (James, 1987; Krantz et al., 1988). Stressors are generally thought to be more abundant in urban industrial environments than in traditional environments (Johansson and Lundberg, 1978; Boyden, 1987), although some might argue that this is an ethnocentric interpretation. Examples of stressors identified in industrial environments include frequent job changes and work overload, which

were associated with CHD incidence in the Framingham study, as well as unskilled or low status jobs making high demands but offering little control, which have been shown to increase the risk of cardiovascular disease (Karasek and Theorell, 1990). Furthermore, many of the social changes associated with modernisation are considered to be stressors. Dressler (1995) has reviewed these stressors and shown how exposure to them has been linked to elevated blood pressure and serum lipid levels in Samoans (Baker et al., 1986) and in his own studies of lifestyle incongruity (Dressler, 1982; Dressler et al., 1993). Stress is a socially constructed phenomenon and it is therefore difficult to make generalisations about what causes stress and it is particularly hard to quantify. Nevertheless, consistent patterns linking processes such as loss of kinship bonds and entry into wage labour in larger scale societies to elevated blood pressure seem to emerge from these studies (Dressler, 1995).

In laboratories, people who say they feel stressed exhibit physiological changes which, if repeated chronically, are thought to increase the risk of CVD. The classic responses identified early in the century are those of epinephrine (Cannon, 1914) and cortisol (Selye, 1956). The secretion of epinephrine, a catecholamine, is controlled by the sympathetic nervous system. It stimulates the release of metabolites that can be used to provide immediate sources of energy, such as glucose and free fatty acids, in the evolutionarily adaptive "fight or flight" mechanism, as well as raising blood pressure. In addition, it causes platelets to become more cohesive, increasing the risk of thrombosis (Fuster et al., 1992b). Lipolysis associated with stress is likely to lead to increased serum cholesterol levels. Indeed, infusions of epinephrine have been shown to raise both free fatty acid and lipoprotein levels (McCann et al., 1995). Studies have shown that epinephrine levels are higher in Samoans living in an urban environment than in a rural environment (James et al., 1985), and in Tokelauans living on Fakoaofo compared to residents of Nukunonu, a nearby island less influenced by a wage economy (Jenner et al., 1987). James et al. (1989) provide a useful review of anthropological studies of catecholamine variation. Cortisol has similar effects on blood pressure and fatty acid levels, and excessive cortisol production has been linked to abdominal fat deposition (Bjorntorp, 1988). However, it is not yet clear that cortisol is consistently elevated in "real-life" stress experienced on a daily basis (Pollard, 1995).

### Smoking

Smoking tobacco is an important risk factor for CVD, and is increasingly recognised as the most important target for public health campaigns aimed at reducing CVD rates. Smoking is the most important known cause of raised fibrinogen levels (Ernst and Resch, 1993; De Boever et al., 1995) and it increases platelet cohesiveness and raises catecholamine levels and thus blood pressure (Kannel, 1987). Muscat et al. (1991) demonstrated that smokers had higher total cholesterol levels than non-smokers, perhaps because nicotine causes enhanced lipolysis. They also note that smoking may have an anti-estrogenic effect.

Smoking is considered to be the dominant risk factor for coronary heart disease in young women because of its increasing prevalence amongst this group in many western countries (Brezinka and Padmos, 1994). It is also important in many groups undergoing economic modernisation. For example, smoking is generally more common among Native Americans and Alaskan Natives than among other ethnic groups in the United States (Ellis and Campos-Outcalt, 1994). However, data collected by Howard et al. (1995) warn against simple generalisations. They found a much higher frequency of smoking amongst Native Americans in the Dakotas and Oklahoma than in Arizona, for example. Native Americans in Arizona also had a significantly lower rate of coronary heart disease and Howard et al. (1995) suggest that part of this difference might be accounted for by smoking habits. Ellis and Campos-Outcalt highlight the fact that smoking may not be the only method of tobacco consumption amongst groups undergoing industrialisation—it is also important to collect data on passive smoke exposure, tobacco chewing and snuff use.

## NEWER HYPOTHESES

Investigations into causes of CVD have focused on adult lifestyle in recent years. In addition to these now widely recognized lifestyle risk factors, medical science has begun to identify other risk factors for CVD, which may suggest an origin earlier in development.

### Undernutrition in early life

Studies conducted in Western populations have demonstrated an inverse correlation between birth weight and other measures of retarded intrauterine growth, and blood pressure in later life in men and women (Barker et al., 1989, 1990; Martyn et al., 1995; Campbell et al., 1996; Leon et al., 1996) and in children (Whincup et al., 1995; Rona et al., 1996) and in a meta-analysis of published studies (Law and Shiell, 1996). Similarly, adult serum cholesterol levels have been shown to be inversely related to abdominal circumference at birth (Barker et al., 1993b). In British men fibrinogen concentrations were inversely related to weight at 1 year of age, after controlling for cigarette smoking, and glucose tolerance decreased with decreasing birth weight (Hales et al., 1991; Barker et al., 1992). In a sample of British men and women thinness at birth was associated with insulin resistance in adult life (Phillips et al., 1994). Furthermore, low birth weight has been associated with greater abdominal obesity in British men and US men and women (Law et al., 1992; Valdez et al., 1994). Not surprisingly, then, there is also an inverse correlation between low birth weight and death from CVD (Barker et al., 1989; Osmond et al., 1993; Martyn et al., 1996). The samples used and relationships identified in these studies are summarised in Table 1.

These correlational studies have been criticised on the grounds that the associations could result from the confounding effects of poverty (Ben-Shlomo and Smith, 1991; Elford et al., 1992; Wannamethee et al., 1996). Within industrial societies, CVDs are most common in those of low socioeconomic status. These people are also more likely to have been born to poorer mothers at a low birth weight. Thus the association observed does not necessarily imply any causal link between retarded intrauterine growth and cardiovascular disease. It is extremely difficult to control for such confounding effects in a manner which still allows the hypothesis to be tested, although some of the published studies have attempted to do so. For example, Koupilová et al. (1997) controlled statistically for sociodemographic characteristics at age 50 in the sample for which Leon et al. (1996) reported an association between birth weight and blood pressure, and found that the relationship remained statistically significant. Kramer and Joseph (1996) also suggest that inconsistencies in the various relationships reported between aspects of fetal growth and different cardiovascular risk factors should give cause for concern. Most recently, Churchill et al. (1997) have shown that blood pressure in pregnant women was inversely correlated with birth weight in an inner-city British population. The authors suggest that "maternal blood pressure may therefore be an important confounding factor in the reported associations between fetal growth retardation and adult hypertension and cardiovascular disease." Convincing evidence regarding causal mechanisms linking intrauterine growth retardation and later cardiovascular disease is needed.

Barker and colleagues have proposed a number of causal mechanisms, although these remain largely speculative. Where gestational age is known and controlled for statistically in analyses, it does not explain these findings, so they cannot be attributed to problems in those born at low weight because they are born prematurely (e.g., Barker et al., 1990, 1993; Martyn et al., 1996). Instead it seems likely that poor maternal nutrition which curtails fetal growth could affect physiological mechanisms controlling serum lipids, fat deposition, insulin resistance and blood pressure later in life (Edwards et al., 1993; Forrester et al., 1996). Such effects are known in other animals (Law and Barker, 1994). Specifically, maternal undernutrition in late pregnancy leading to reduced (compared to modern industrial norms) liver growth and reduced abdominal circumference at birth has been proposed as the mechanism lead-

*TABLE 1. Significant findings in studies relating measures of intrauterine growth for individuals with later CVD related outcomes*

| CVD related outcome | Measure of retarded intrauterine growth | Location | Sample size | Composition | Reference |
|---|---|---|---|---|---|
| BP | Birth weight, placental weight | Lancashire, UK | 449 | Men and women | Barker et al., 1990 |
| BP | Birth weight | Uppsala, Sweden | 1333 | Men | Leon et al., 1996 |
| SBP | Birth weight | UK | 1987 | Children, both sexes | Rona et al., 1996 |
| SBP | Birth weight | UK | 9921 | Children, both sexes | Barker et al., 1989 |
| SBP | Birth weight | UK | 3259 | Men and women | Barker et al., 1989 |
| SBP | Birth weight | Aberdeen, UK | 253 | Men and women | Campbell et al., 1996 |
| SBP | Birth weight | Kingston, Jamaica | 1610 | Children | Forrester et al., 1996 |
| BP, arterial compliance | Birth weight, length, abdominal and head circumference | Sheffield, UK | 337 | Men and women | Martyn et al., 1995 |
| BP, impaired glucose tolerance | Birth weight | Hertfordshire, UK | 468 | Men | Hales et al., 1991 |
| Waist to hip ratio | Birth weight | UK | 1084 | Men | Law et al., 1992 |
| Fasting insulin, abdominal fat | Birth weight, length, head circumference | San Antonio, USA | 564 | Men | Valdez et al., 1994 |
| Coronary heart disease | Birth weight | Mysore, India | 517 | Men and women | Stein et al., 1996 |
| CVD mortality | Birth weight | Hertfordshire, UK | 15 726 | Men and women | Osmond et al., 1993 |
| Stroke and coronary heart disease mortality | Birth weight | UK | 13 249 | Men | Martyn et al., 1996 |
| Fibrinogen concentration | Ratio of placental weight to birth weight | Lancashire, UK | 148 | Men | Barker et al., 1992 |
| Total cholesterol, LDL, Apoprotein B | Abdominal circumference at birth | Sheffield, UK | 219 | Men and women | Barker et al., 1993 |

Main findings for each paper are recorded. Significant findings for measurements at 1 year of age, and non-significant findings are not recorded. BP = blood pressure, both systolic and diastolic, SBP = systolic blood pressure.

ing to changes in cholesterol metabolism in the liver (Barker et al., 1993a). Martyn et al. (1995) suggest that effects on blood pressure may result from modification of arterial structure in response to undernutrition in fetal life, leading to reduced arterial compliance and cumulative increases in blood pressure in later life. Alternatively, Mackenzie and Brenner (1995) suggest that the association between low birth weight and high blood pressure may be explained by the development of fewer nephrons in low birth weight babies. It is reasoned that having fewer nephrons reduces total renal excretory capacity, and particularly the capacity to excrete sodium.

Leon et al. (1996) found that adjustment for insulin resistance led to a moderate reduction in the strength of the relationship between birth weight and blood pressure in their sample of Swedish men. It is possible, therefore, that fetal experiences which have permanent consequences for insulin mediated carbohydrate metabolism, and low glucose tolerance in particular, might explain part of the association (Hales and Barker, 1992; Desai et al., 1995). Reduced fetal growth is also a risk factor for diabetes (McCance et al., 1994; Lithell et al., 1996). Hales and Barker (1992) have proposed that undernutrition might affect development of pancreatic cells, since they normally develop rapidly in fetal life. They suggest that lack of amino acids in the maternal diet may be the critical factor affecting pancreatic cells. These effects may not be limited to fetal life; for example, studies of malnourished children have demonstrated a permanent reduction of insulin response to glucose (Hales and Barker, 1992).

According to Barker, the stage of gestation at which growth retardation occurs is important. He suggests that slow growth early in gestation, leading to proportionate small size, can protect the fetus from the effects of undernutrition later in gestation, which give rise to disproportionate growth (Barker, 1996). He explains the low rates of coronary heart disease in countries such as China, where low birth weights are common, in this way (although China may not have been a good example to choose, since almost 30% of all deaths there are caused by cardiovascular diseases; Lopez, 1993). An alternative suggestion, espoused by Barker elsewhere (Hales and Barker, 1992), is that low birth weight only carries a greater risk of cardiovascular disease in those who encounter classic lifestyle risk factors in later life. This idea was proposed by Forsdahl (1977) based on geographical correlations between infant mortality rates and death rates from ischemic heart disease in Norway. Forsdahl explicitly suggested that nutritional deprivation in childhood followed by relative affluence results in an increased risk of cardiovascular disease.

Leon et al. (1996) provide evidence that blood pressure correlations with indicators of fetal growth are strongest in individuals who are well nourished later in life. That is, individuals who do not reach their full growth potential in utero are at risk of developing high blood pressure in later life particularly if they have a high body mass index. Phillips et al. (1994) showed that people who were thin at birth but obese as adults were most resistant to insulin in their sample of British men and women. Most, if not all, of the studies showing a relationship between fetal growth and cardiovascular disease or cardiovascular risk factors appear to have been conducted in populations which are now relatively well nourished and the vast majority have been conducted in Europe. In addition, Forrester et al. (1996) reported an inverse correlation between birth weight and blood pressure in Jamaican children and a trend towards a similar relationship for serum cholesterol. Stein et al. (1996) found a higher prevalence of coronary heart disease with low birth weight in the city of Mysore in India, where the adults are described as relatively well nourished. The fact that the grown women in the sample had a mean weight of 57 kg, whereas the mean weight of their mothers during pregnancy was 47 kg, suggests that the generation who formed the focus of the study were better nourished than their parents.

Barker's group has also shown that men who were breast-fed beyond 1 year of age had higher serum total and LDL cholesterol levels than other men born between 1920 and 1930 in Hertfordshire, England (Fall et al., 1992). One explanation of this phenomenon extends the reasoning developed for explanations of the effects of the fetal environment. It has been suggested that the relatively low fat and energy levels provided by breast-milk compared to western solid foods may program the activity of enzymes controlling cholesterol synthesis and excretion such that later encounters with a high fat diet increase risk of cardiovascular disease (Barker et al., 1993b).

These proposed effects of fetal and infant environment on later metabolism may or may not be regarded as evidence of adaptive developmental plasticity. Fetuses of under- or marginally nourished mothers may have a metabolism adapted to cope with a poor environment, using fats, for example, in a metabolically efficient manner. Such a strategy is adaptive when environments are stable. When environments rich in carbohydrates and fat are encountered later in life such efficiency may lead to high blood pressure and cholesterol levels, and insulin resistance. Thus, this developmental adaptation can be regarded as resulting in a thrifty phenotype, with the same effects as those proposed for the thrifty genotype (Neel, 1962). Barker and colleagues have proposed a weak version of this adaptive hypothesis. Barker et al. (1993a) suggested only that impaired growth of beta cells and islets of Langerhans in the pancreas and other metabolic changes may serve a short-term adaptive purpose in allowing the neonate to survive undernutrition. Hales and Barker (1992) proposed that these changes will not cause problems so long as the individual lives in an environment in which there is no need to produce much insulin, but may create difficulties if the individual is exposed

to a more western diet. Thus the thrifty phenotype could be regarded as an adaptive fetal response which may have arisen because of its selective advantages, or it can be regarded simply as a once unproblematic by-product of fetal malnutrition.

Supporters of the thrifty genotype hypothesis have suggested an alternative explanation for the link between low birth weight and later risk of diabetes. McCance et al. (1994) observed a greater risk of non-insulin dependent diabetes in Pima Indians of low birth weight. They proposed that, given the higher risk of mortality for low birth weight infants, people of low birth weight in their sample represent a selected group who survived better as infants in a nutritionally impoverished environment because of their genetic tendency towards insulin resistance. If this mechanism operated over several generations it would ultimately lead to the predominance of a thrifty genotype in the population (McCance et al., 1994). This of course, is the central tenet of the thrifty genotype hypothesis, which has been used to explain the very high prevalence of non-insulin dependent diabetes in Pima Indians, amongst others.

The difference between the two explanations is that the first relies on a species-wide developmental plasticity, which has been termed environmental programming, whereas the latter implies that only certain individuals, concentrated largely in certain populations, show such thriftiness. It is, of course, possible, and even likely, that both mechanisms occur. However, the thrifty phenotype hypothesis does offer an attractive alternative explanation to the thrifty genotype model. It might explain why the experience of obesity, diabetes and, often, cardiovascular disease, is so common in a variety of populations that have undergone rapid modernisation. If low birth weight is an important risk factor, and is most important in those whose environment changes, we might expect to see high rates of disease in newly modernising societies, particularly those which have undergone rapid change.

Disentangling the effects of thrifty genotypes and thrifty phenotypes will be difficult. The most obvious test will be an examination of the prevalence of cardiovascular disease in different cohorts, born before, during and after large-scale environmental changes, if birth weights change as might be expected. Certainly, American Samoan and Native American infants now have high average birth weights (Bindon and Zansky, 1986), although birth weights of Australian Aborigines are significantly lower than those for Australians of European origin (Kirk, 1981) (and one small study has shown that a central pattern of fat distribution was associated with lower birth weight in Australian Aborigine children; Dugdale and Lovell, 1981). Most often surveys include only older individuals and so will miss such intergenerational effects (e.g. Howard et al., 1995).

An interesting case study is provided by the inhabitants of the island of Nauru (Hales and Barker, 1992). Zimmett et al. (1977) reported that the prevalence of diabetes in the Pacific island of Nauru was 34% in individuals over 15 years old. Affluence and westernisation had come to this population suddenly as a result of phosphate mining after World War II. Most of these adults were therefore born in times of relative undernutrition but later lived in an environment providing a plentiful diet. Recently Dowse et al. (1991) reported a decline in the prevalence of impaired glucose tolerance on Nauru (although total cholesterol levels increased). Dowse et al. (1991) attributed this decline to the fact that the most genetically susceptible individuals had already succumbed so that, in the absence of further lifestyle change, no further increase in symptoms would be expected. It is also possible, of course, that it was the individuals most phenotypically susceptible because of early environmental influences who were the ones who had already developed glucose intolerance. At the time of the survey by Dowse et al., no age-related effects in the decline were strongly apparent, although their figures suggest that the youngest age groups may have shown the greatest fall in risk of impaired glucose tolerance. It will be interesting to see whether future generations, if they achieve greater birth weights, show a reduced susceptibility.

A related hypothesis concerns the effects of fast growth, that is, growth in childhood that exceeds the rate of that which would

have occurred in what Boyden (1987) called the primeval phase. Weder and Schork (1994) suggested that somatic growth typical of children in modernising or modern industrial societies puts a strain on renal function because growth of the kidneys does not match growth in weight. They write that "since body fluid volumes and electrolyte content are closely and directly proportional to body weight, normal allometric scaling may result in kidneys too small to maintain fluid and electrolyte homeostasis without the added compensation of higher blood pressure." As with the low birth weight hypothesis, it is not absolute size that affects blood pressure, but an increase in size relative to "expected" size (this time that "expected" during evolution of patterns of growth). Interestingly, this hypothesis predicts higher blood pressure in those who grow fast, but not higher cholesterol levels.

It seems clear that we need to take account of the effects of early nutrition and growth when investigating risk factors for cardiovascular disease in non-industrial as well as industrial societies. Those who have been "programmed" for low-energy, low-fat diets may be at especially high risk of cardiovascular disease if they are exposed to high-energy, high-fat diets in later life. Obviously studies such as those conducted by Barker and colleagues are much more difficult to achieve in situations where records of birth weight are not always available. A second-best proxy is adult height which is at least partly determined by early environment and has also been shown to be inversely related to CVD (Elo and Preston, 1992).

We should also consider the policy implications, and concentrate efforts to ensure that maternal nutrition is adequate in all populations. Kuh and Smith (1993) point out that such a perspective is not new—a public health focus on early life was common in the first half of the 20th century, but was largely superseded after World War II. Cameron (1996) notes that among "the majority of women in developing countries, small body size due to chronic malnutrition during childhood, low energy reserves due to close birth spacing, and relatively high levels of activity throughout pregnancy, suggest that food supplementation would be effective in increasing birthweight."

## Infectious diseases

Suspicions that infectious processes might play a role in atherosclerosis (Lopes-Virella and Virella, 1985) have recently been boosted by work, mostly conducted in Europe, showing that people with coronary heart disease have a higher prevalence of infection with certain bacteria than do controls (Saikku et al., 1988, 1992; Thom et al., 1992; Linnanmäki et al., 1993; Mendall et al., 1994; Murray et al., 1995; Patel et al., 1995; Aceti et al., 1996; Niemelä et al., 1996; Scragg et al., 1996; Whincup et al., 1996), with few null findings having been reported (Rathbone et al., 1996, is a rare example). The two bacteria so far implicated are *Helicobacter pylori* and *Chlamydia pneumoniae,* a species only identified in the 1980s. Both are widespread and common infections, *H. pylori* causing gastric symptoms and already firmly implicated in peptic ulcer disease and probably gastric cancer, and *C. pneumoniae* causing a variety of upper respiratory infections and 5–10% of pneumonia cases worldwide (Saikku et al., 1992). Patel et al. (1995) deduce from the results of their study that between one-third and one-half of coronary heart disease in men in the general population of London could be attributable to either or both of these infections.

Saikku and co-workers reported some of the earliest findings. In their first, widely cited paper (Saikku et al., 1988) they compared data from 40 middle-aged men from the Helsinki area who had suffered an acute myocardial infarction and 30 men with chronic coronary heart disease with those from 41 controls, matched for sex, age, time and locality. Chronic infection with *Chlamydia pneumoniae* was assessed using tests for raised *C. pneumoniae* antibody (IgA and IgG) titres. The rate of infection was significantly higher in the patients with heart disease. However, because of the cross-sectional design of this study, the authors could not exclude the possibility that heart disease might activate latent *C. pneumoniae* infection. They therefore took advantage of data collected for the Helsinki Heart Study in a later paper, which allowed them to

examine rates of infection from a larger number of men (103 patients with cardiac events and 103 healthy controls, matched for treatment, locality and time). Analysis of serum samples collected 3 to 6 months before a cardiac end point again showed raised antibody levels in the patients.

As with low birth weight, it is possible that seropositivity for these bacteria is associated with other risk factors linked with poverty in industrialised countries, which account for the association with cardiovascular disease. Such concerns are raised by findings that correction for social class or physiological risk factors, including cholesterol levels and blood pressure, greatly reduced associations between infection and disease in some studies (Niemalä et al., 1996; Whincup et al., 1996), and also by findings that smoking appears to increase risk of infection with *C. pneumoniae,* as well as risk of CVD (Karvonen et al., 1994). Some studies have, however, corrected statistically for a comprehensive range of such factors and still found an association (e.g., Saikku et al., 1992; Linnanmäki et al., 1993). It is crucial that the putative mechanisms linking these factors are elucidated. Suggested mechanisms include the possibilities that chronic inflammation may increase risk of cardiovascular disease, and that bacterial components may form immune complexes with antibodies which can lead to endothelial injury. Most attention has been paid to the former possibility.

Patel et al. (1995) suggest that persistent inflammatory responses associated with chronic infections by these organisms may contribute to the risk of coronary heart disease. The actions of acute phase proteins, including fibrinogen, C reactive protein and serum amyloid A may play a direct role, and may also act as markers of other mechanisms linked with inflammation. In support of its hypothesis, this group has shown that higher concentrations of C reactive protein, which is a sensitive marker of systemic inflammation, were associated with *C. pneumoniae* and *H. pylori* seropositivity in British men (Mendall et al., 1996). In turn, concentrations of C reactive protein were positively correlated with total cholesterol level and fibrinogen, and negatively correlated with HDL cholesterol level (as is infection with *H. pylori;* Niemalä et al., 1996; Whincup et al., 1996). Scragg et al. (1996) also found an inverse relationship between C reactive protein levels and HDL cholesterol, in a workplace survey in New Zealand. The same relationships are seen in acute responses to illness when C reactive proteins are greatly elevated (Steel and Whitehead, 1994). In contrast, Kuller et al. (1996) report only weak associations between C reactive protein and blood pressure and cholesterol levels, but they also found a significant association between C reactive protein levels and later death from coronary heart disease. Grau et al. (1996) report that people who had a history of cerebrovascular or cardiovascular disease had higher C reactive protein levels than people without disease.

The production of C reactive protein is regulated by cytokines and Mendall et al. (1996) suggest that the associations seen between C reactive protein concentration and cardiovascular risk factors are indirect and could be explained by other actions of cytokines, particularly interleukin 6. For example, interleukin 6 can increase hepatic synthesis of clotting factors. Fibrinogen and serum amyloid A may act to increase risk directly. We have already seen that raised fibrinogen increases risk of ischemic heart disease, and infection with either *H. pylori* or *C. pneumoniae* has been shown to be associated with raised fibrinogen levels (Patel et al., 1994). Serum amyloid A is thought to associate with HDL particles, diminishing their capacity to mediate reverse cholesterol transport (Steel and Whitehead, 1994). Chronic inflammation also increases the risk of ischemia by stimulating the coagulation system directly (Grau et al., 1996). However, it is possible that raised levels of acute phase proteins are caused by inflammation in the arterial wall associated with atherosclerosis, implying that the causality of the relationship is the reverse of that postulated by Patel et al. (1995).

A completely different mechanism for the apparent link between *H. pylori* and cardiovascular disease was proposed by Sung and Sanderson (1996). They note that, as a result of gastric dysfunction and malabsorp-

tion, *H. pylori* can cause nutritional deficiency, especially of vitamins B6, B12 and folate. They also draw attention to findings that deficiency in these vitamins can lead to elevated levels of the amino acid homocysteine. Hyperhomocysteinemia results in a high risk of premature atherosclerosis and venous thrombosis (Fuster et al., 1992b). The mechanism for this effect is not fully understood, but homocysteine is known to be toxic to endothelial cells (Sung and Sanderson, 1996). Thus it is possible that *H. pylori* infection may increase risk of cardiovascular disease by inhibiting absorption of these vitamins (Fig. 3). If this mechanism is important, *H. pylori* is likely to carry differential risk in different populations according to dietary patterns and propensity for vitamin B6, vitamin B12 and folate deficiency. Other possible mechanisms linking chronic infection and atherosclerosis are reviewed by Lopes-Virella and Virella (1985) and Saikku et al. (1992). Prospective studies are needed to disentangle the causality of these fascinating relationships.

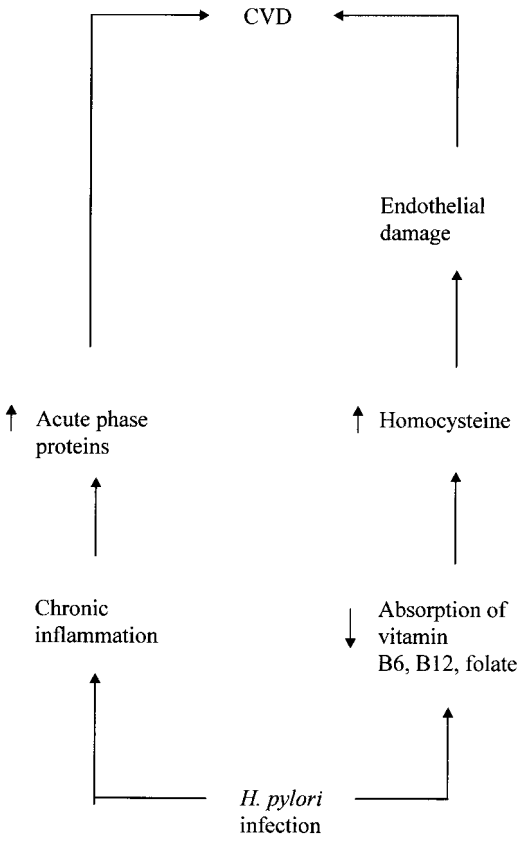


Fig. 3. Hypothesised links between *H. pylori* infection and cardiovascular disease (adapted from Sung and Sanderson, 1996).

Clearly, if these two pathogens, and thus quite possibly others which result in chronic infections and chronic inflammation (e.g. herpes virus; Sorlie et al., 1994), do have a major role to play in coronary heart disease (and possibly other forms of CVD), there are important implications for our understanding of who is at risk. It has been argued that *H. pylori* is the most common chronic bacterial infection in humans (Luzza et al., 1995) and *C. pneumoniae* is also very common, so if they are implicated in the etiology of cardiovascular disease, their impact could be enormous. For example, Webb et al. (1994) cite figures suggesting that around 50% of adults may be infected with *H. pylori* in developed countries, whereas 90% of adults may be infected in developing countries. *Chlamydia pneumoniae* is thought to have a prevalence of about 50% in middle-aged adults throughout the world. Again, prevalence increases with age and in Scandinavian countries at least, there are widespread epidemics every 4 to 5 years (Saikku et al., 1992).

Knowledge of the epidemiology of these two infections may throw light on their likely importance for cardiovascular disease in different populations and sectors of populations. Of the two, most is known about *H. pylori*. It is thought mainly to spread via the fecal-oral route, but water-borne transmission is possible, and likely to be more important in areas with heavily contaminated water supplies, as indicated by findings from Peru (Goodman and Correa, 1995). There is good evidence that infection with *H. pylori* is usually acquired during childhood and that it is more common in people living in crowded environments. For example, Webb et al. (1994) showed that amongst British factory workers, those who had grown up in crowded households (more than one person per living room) or who had regularly shared a bed in childhood were significantly more likely to show seropositivity for *H. pylori*. Mendall et al. (1992) found that the absence of hot

water and presence of overcrowding in the childhood home were significant predictors of seropositivity in adults in London. In a sample from Wales, Galpin et al. (1992) found that seropositivity was more common in manual workers and in those who shared a bed as a child. Such differentials within an industrial society have led to the suggestion that infection with *H. pylori* may account for social class differentials in cardiovascular disease which cannot be accounted for by classic risk factors, although Murray et al.'s (1995) study in Northern Ireland did not support this hypothesis. There is also evidence for cohort effects. For example, in Japan prevalence rates were consistently 70–85% in those born before 1950, but only about 5% in 0–6-year-olds and 45% in 30–39-year-olds in the mid-1980s, which is much lower for this age group than might be expected from the figures for older adults (Asaka et al., 1992). Such effects may help explain declining rates of cardiovascular disease in richer countries.

High prevalence rates of these two bacterial infections in poorer countries undergoing rapid economic change, which is likely to introduce classic risk factors, may well give reason for concern. For example, prevalence rates in Southern China were greatest in an urban area, where classic risk factors are more prevalent (Mitchell et al., 1992). Indeed, it is possible that infection with these bacteria is only important in environments where the classic lifestyle risk factors are found, particularly if, as seems likely, risk is increased through pathways associated with cholesterol and atherosclerosis. If so, this would help explain the deficit in cardiovascular disease in populations where infection is more common but other risk factors largely absent. As with low birth weight, however, some populations undergoing socioeconomic change may be at particularly high risk because of a combination of risk factors from the old and new environments. This will be particularly true for the older generation, and for those in populations where classic risk factors come into play whilst infectious disease is still rife, such as Australian Aborigines. It is noteworthy that Scragg et al. (1996) found that seropositivity varied with ethnic group in New Zealand. Pacific Islanders had a rate of infection (73%) more than twice that of Europeans (36%), whilst Maoris had intermediate infection rates of 57%, perhaps partly because Pacific Islanders were more likely to be migrants from poorer countries where they could have acquired the infection during childhood. Rates of coronary heart disease are still low in Pacific Islanders compared to the rest of the New Zealand population, but they are raised amongst Maoris. These differences are hard to explain using classic risk factors (Scragg et al., 1993) and this is one case where infection and classic risk factors may be interacting in a complex manner.

More studies are needed, but at present are hampered by difficulties in assessing seropositivity in easily obtained samples. Advances in this field may allow diagnosis to be made from specific immunoglobulin G levels in saliva (Luzza et al., 1995).

### Sex differences

In populations with high rates of CVD, women generally suffer less CVD morbidity and mortality than men (Haffner and Valdez, 1995). Women in these populations have a healthier serum lipid profile than men, including higher levels of HDL cholesterol, and lower blood pressure than men (Shively et al., 1993). Some of this difference is almost certainly attributable to behavioural factors and what we may term gender differences because they are not biologically determined by sex. There is good evidence that gender differences in exposure to risk factors are important in modernising societies. For example, women tend to score lower on indices of modernisation (Schall, 1995) and women are often much less likely to drink alcohol or smoke tobacco than men (e.g. in India, Stein et al., 1996; in Fiji, Toren, 1994; in the United States, Hall, 1994; in Native Americans, Campos-Outcalt et al., 1995). Intriguingly, prevalence of seropositivity for *C. pneumoniae* tends to be higher in men than in women (Karvonen et al., 1994), and Replogle et al. (1995) reported a higher prevalence of *H. pylori* infection in men than in women in a survey of healthy young adults in California, and find evidence for the same effect in a meta-analysis of previous studies in other populations.

These authors suggest that men are at greater risk of infection by *H. pylori* as adults because they are more likely to participate in activities involving close physical contact; if this phenomenon is confirmed, it is likely to be culture-specific and can be regarded as an effect of gender rather than of sex. However, biological differences between men and women, are also likely to be important.

McGarvey (1994) notes that within Polynesian populations undergoing economic modernisation women are generally fatter than men. He cites gender differences in exposure to education and employment as possible causes and these are clearly important. Janes (1990) writes in detail about changing gender roles in a Samoan population. He also posits sex differences which may explain this apparent difference between men and women in weight gain in response to environmental change, suggesting that greater metabolic efficiency in women associated with a greater need for fat storage (to sustain pregnancy and lactation) could make them more susceptible to weight gain when diets become more calorific. We have already seen, however, that weight gain in these populations has, as yet, not been associated strongly with mortality risk (Baker and Crews, 1986).

Women's risk of CVD increases after menopause and there is now good evidence that the reason for this is a drop in estrogen levels (Knopp et al., 1994; Haffner and Valdez, 1995). Estrogen, therefore, appears to protect women from cardiovascular disease. Further evidence that this is so comes from studies of women receiving hormone replacement therapy, who show a reduced risk compared to unmedicated women (Stampfer and Colditz, 1991).

Estrogen acts in a variety of ways to decrease risk of cardiovascular disease (Farhat et al., 1996). It appears to decrease triglyceride and LDL cholesterol levels and to increase HDL cholesterol (Haffner and Valdez, 1995), and Barrett-Connor and Laakso (1990) have shown that estrogen use is associated with lower insulin concentrations in postmenopausal women. It also appears to affect mechanisms controlling vasoconstriction in a beneficial way and to act as an antioxidant (Knopp et al., 1994; Chester et al., 1995). In addition, estrogen inhibits vascular smooth muscle cell proliferation, an important stage in atherosclerosis (Karas et al., 1994). Recent evidence suggests that it may provide protection by enhancing levels of nitric oxide synthesis in the endothelium. Kharatinov et al. (1994) found that exhaled nitric oxide levels were highest in women during the middle of the menstrual cycle, when estrogen levels are at their peak. Both Rosselli et al. (1995) and Cicinelli et al. (1997) have shown that serum markers of nitric oxide levels were increased in postmenopausal women given estradiol.

Furthermore, it seems that estrogen can buffer the effects of psychosocial stress on cardiovascular risk factors (Matthews, 1989). Laboratory investigations have examined the effects of exogenous estradiol on responses to stress in women and men and have compared responses to stress in premenopausal and postmenopausal women. The first approach has produced evidence suggesting that exogenous estrogen can blunt the sympathetic-adreno-medullary response to stress (Lindheim et al., 1992; del Rio et al., 1994) while the second has shown that the blood pressure and epinephrine responses of postmenopausal women to laboratory stressors appear to be greater than those of premenopausal women (Saab et al., 1989; Lindheim et al., 1992). It is not completely clear how estrogen can produce such effects, but a number of possible mechanisms have been identified. For example, estrogens affect the sympathetic nervous system in several ways, by influencing the activity of catecholamine-synthesising enzymes and catecholamine-degrading enzymes as well as adrenoceptor activity (del Rio et al., 1994). Their effects on lipoprotein metabolism during psychosocial stress may be beneficial, for example increasing the rate of clearance of LDL cholesterol.

The high levels of estrogen found in women in industrial and industrialising societies are likely to be an evolutionarily new phenomenon, partly because of changes in fertility patterns and partly because of changes in ovarian function (Worthman, 1995). The "primeval phase" (Boyden, 1987) pattern of fertility is thought to have approximated

that of present-day foragers, who have a total fertility rate (total number of live births for women) of about 5.6 (Bentley et al., 1993). Women would have attained menarche later than is normal in industrial societies today and would have spent much of the time until menopause either pregnant or (mostly) breast-feeding. High levels of estrogens are secreted by the placenta towards the end of pregnancy, but levels are low during lactation and suppression of the ovarian cycle, which probably lasted up to 4 years after each birth (Konner and Worthman, 1980). In contrast, women in industrial societies today experience menarche at comparatively early ages (Eveleth and Tanner, 1990) and low fertility, often breast-feeding for only a few weeks or not at all. Women thus experience many more ovarian cycles and associated fluctuations in estrogen level than used to be the case. Most recently, large numbers of women have begun to take synthetic estrogen to ward off unpleasant symptoms associated with the menopause, artificially extending their cycles and their exposure to estrogen. Ellison et al. (1993) have also shown that ovarian function, as assessed by serum and salivary progesterone concentrations, is greater in women living in modern industrial societies than it is in women living in traditional societies. Similar findings emerged from a comparison of British and rural Chinese women. Key et al. (1990) reported data showing that at premenopausal ages British women had a mean concentration of estradiol that was 36% higher than Chinese women. One reason for this might be that higher intake of dietary fat is correlated with higher estrogen levels (Goldin et al., 1986).

Thus in a modern environment women are often exposed to higher levels of endogenous estrogen than previously, and therefore increase their protection from risk factors such as a westernisation of diet, reduction in physical activity, and psychosocial stress. The same process may operate in women whose environment undergoes rapid economic change during their lifespan. However, Ellison (1996) has proposed that differences in adult gonadal function may be at least partly due to developmental processes operating during childhood and adolescence to establish adult set-points of the hypothalamic-pituitary-gonadal axis, in which case these women would not be as well protected as women living in a more stable industrial environment.

According to these ideas, women of reproductive age should in general show a smaller increase in risk of cardiovascular disease associated with economic and environmental change than men with equivalent exposure to environmental risk factors, because the protection provided by estrogen is likely to increase at the same time. However, women who have spent their early years in a more traditional environment may not experience this protection in a rapidly changing environment.

Given the profound importance of gender differences in all societies it is highly unlikely that men and women will be exposed to the same environmental changes, making these hypotheses difficult to test. However, there is evidence that blood pressure rises more with modernisation in men than in women of reproductive age. Data recently collected from two traditional villages in Tanzania show that blood pressure was slightly higher in women at all age groups until age 65, in contrast to the pattern seen in industrialised populations (Pauletto et al., 1996). Schall (1995) compared blood pressure in Manus islanders of Papua New Guinea who lived as subsistence farmers and fishers in villages with migrants to towns and cities who were integrated into the cash economy. In men blood pressure increased from villages to towns to cities, but in women this effect was not seen, even though both sexes showed gradated increases in obesity. Across Pacific populations, the typical pattern of higher blood pressure in young men than in young women was accentuated for adults living in modern environments (Schall, 1995). Similarly, visual inspection of the worldwide data compiled by Pollard et al. (1991) suggests that young men show a greater increase in blood pressure with modernisation than young women, resulting in an increasing differential in this age group. Furthermore, Chin-Hong and McGarvey (1996) reported that lifestyle incongruity was related to blood

pressure amongst Western Samoan men, but not amongst young women. Inspection of results of a survey investigating links between modernisation and serum lipid levels in Papua New Guinea suggests that among younger women LDL cholesterol levels were greater in women than in men in the most traditional populations, but greater in men in the more modernised populations (Hodge et al., 1996).

In contrast, Kunitz (1994) reported data showing that amongst Navajo women aged 65 or older, but not men, hypertension has become more common since the 1950s and that amongst women, but not men, hypertension was associated with greater education and social isolation. He suggests that gender differences are very important here. Data from younger women were not reported, but these results are consistent with worldwide results showing that at older ages, women have higher blood pressure than men (Pollard et al., 1991). Perhaps, in addition to gender effects, the loss of protection provided by estrogen in menopausal women places them at a particularly high risk from environmental changes associated with modernisation.

Sex and gender effects should be of great interest to those investigating the consequences of modernisation for cardiovascular health. They have not received much attention as yet.

## CONCLUSION

Industrial societies are typically characterised by an increased prevalence of a number of important and well-known risk factors for CVDs, such as a high density diet, low levels of physical activity and a high prevalence of smoking tobacco. However, within this broad profile there are many differences between industrial societies, both geographically and over time. Variation in lifestyle within populations in developing countries and modernising populations is also marked. These differences can explain many, but not all, of the trends seen in cardiovascular disease.

To explain inter- and intrapopulation variation in CVD prevalence it is also essential that we expand our horizons beyond the well known risk factors to consider other, newly identified, risk factors (Fig. 4). Several exciting hypotheses regarding some quite different risk factors are currently being tested by medical scientists, and anthropologists can also play an important role here. We have seen that there is evidence that early undernutrition and consequent slow intrauterine, and perhaps infant, growth appears to be a risk factor for cardiovascular disease. It may be that differences between, and changes within, populations in nutritional status at birth and in early childhood can help explain some of the variation in CVD rates which cannot be explained by well-known lifestyle risk factors. The role of infectious agents in increasing risk of cardiovascular disease has also recently received increasing attention. In particular, infection with *Chlamydia pneumoniae* or *Helicobacter pylori* has been linked to an increased risk of coronary heart disease. In future studies it will be important to take into account differences in the prevalence of such disease organisms when examining population and individual risk of CVD. Nutritional status and infectious disease ecology have long been of interest to physical anthropologists and expertise in these areas can now be applied to improving our understanding of degenerative CVDs.

Sex differences are an important source of variation in CVD risk, and evidence points to a role for biological mechanisms in addition to cultural processes. Estrogen seems to have a number of protective effects which may help explain why the CVD experiences of women are very different to those of men. Anthropologists have amassed a great deal of knowledge about ecological variation in estrogen levels which will add to our understanding of women's risk in different populations.

There are good reasons why all these mechanisms will have particularly important effects within modernising populations, particularly amongst those born into a traditional environment with a high likelihood of early undernutrition and of childhood infection with *H. pylori* and *C. pneumoniae*, and of early influences on hormonal set-points which contrast with those born into industrialised populations. These hypotheses all suggest reasons why populations undergoing rapid modernisation should be at particu-

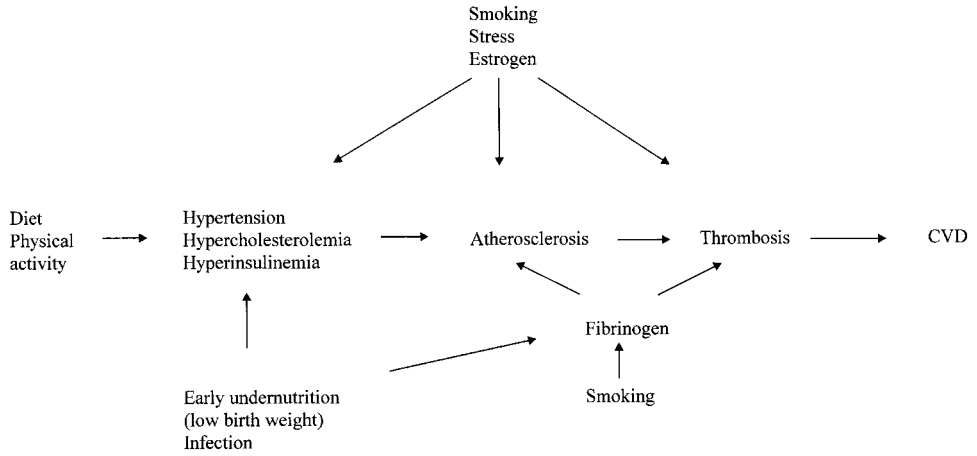


Fig. 4. The putative mechanisms of well-known and newly identified environmental risk factors in the pathogenesis of cardiovascular diseases.

larly high risk of developing physiological profiles associated with CVDs, based on environmental rather than genetic effects. While demanding a great deal of researchers, further studies in populations undergoing environmental change associated with modernisation and development, which incorporate assessment of early nutritional status, infection and sex hormone profiles, will be particularly enlightening.

## LITERATURE CITED

Aceti A, Mazzacurati G, Amendolea MA, Pennica A, and Zechini B (1996) H. pylori and C. pneumoniae infections may account for most acute coronary syndromes. BMJ *313:*428–429.

Anderson EA and Mark AL (1993) The vasodilator action of insulin: Implications for the insulin hypothesis of hypertension. Hypertension *21:*136–141.

Asaka M, Kimura T, Kudo M, Takeda H, Miyazaki T, Miki K, and Graham D (1992) Relationship of Helicobacter pylori to serum pepsinogens in an asymptomatic Japanese population. Gastroenterology *102:*760–766.

Baker PT and Crews DE (1986) Mortality patterns and some biological predictors. In PT Baker, J Hanna, and TS Baker (eds.): The Changing Samoans: Behavior and Health in Transition. New York: Oxford University Press, pp 93–122.

Baker PT, Hanna JW, and Baker TS (eds.) (1986) The Changing Samoans: Behavior and Health in Transition. New York: Oxford University Press.

Barker DJP (1996) The origins of coronary heart disease in early life. In C Henry and SJ Ulijaszek (eds): Long-Term Consequences of Early Environment: Growth, Development and the Lifespan Developmental Perspective. Cambridge: Cambridge University Press, pp 155–162.

Barker DJP, Osmond C, Golding J, Kuh D, and Wadworth MEJ (1989) Growth in utero, blood pressure in childhood and adult life, and mortality from cardiovascular disease. BMJ *298:*564–567.

Barker DJP, Bull AR, Osmond C, and Simmonds SJ (1990) Fetal and placental size and risk of hypertension in adult life. BMJ *301:*259–262.

Barker DJP, Meade TW, Fall CHD, Lee A, Osmond C, Phipps K, and Stirling Y (1992) Relation of fetal and infant growth to plasma fibrinogen and factor VIII concentrations in adult life. BMJ *304:*148–152.

Barker DJP, Gluckman PD, Godfrey KM, Harding JE, Owens JA, and Robinson JS (1993a) Fetal nutrition and cardiovascular disease in adult life. Lancet *341:* 938–941.

Barker DJP, Martyn CN, Osmond C, Hales CN, and Fall CHD (1993b) Growth in utero and serum cholesterol concentrations in adult life. BMJ *307:*1524–1527.

Barrett-Connor E and Laakso M (1990) Ischemic heart disease risk in postmenopausal women: Effects of estrogen use on glucose and insulin levels. Arteriosclerosis *10:*531–534.

Beilin LJ (1992) Dietary salt and risk factors for cardiovascular disease. Kidney Int. *41*(S37):590–596.

Ben-Shlomo Y and Smith GD (1991) Deprivation in infancy or in adult life: Which is more important for mortality risk? Lancet *337:*530–534.

Bentley GR, Jasienska G, and Goldberg T (1993) Is the fertility of agriculturalists higher than that of nonagriculturalists? Curr. Anthropol. *34:*778–785.

Bindon JR and Zansky S (1986) Growth and body composition. In PT Baker, J Hanna, and TS Baker (eds.): The Changing Samoans: Behavior and Health in Transition. Oxford: Oxford University Press, pp 222–253.

Bjorntorp P (1988) Possible mechanisms relating fat distribution and metabolism. In C Bouchard and F Johnston (eds): Fat Distribution During Growth and Later Health Outcomes. New York: Alan R. Liss.

Boyden S (1987) Western Civilization in Biological Perspective: Patterns in Biohistory. Oxford: Oxford University Press.

Brezinka V and Padmos I (1994) Coronary heart disease risk factors in women. Eur. Heart J. *15:*1571–1584.

Cameron N (1996) Antenatal and birth factors and their relationships to child growth. In C Henry and S

Ulijaszek (eds.): Long-Term Consequences of Early Environment: Growth, Development and the Lifespan Developmental Perspective. Cambridge: Cambridge University Press, pp 69–90.
Campbell DM, Hall MH, Barker DJP, Cross J, Shiell AW, and Godfrey KM (1996) Diet in pregnancy and the offspring's blood pressure 40 years later. Br. J. Obstet. Gynaecol. *103:*273–280.
Campos-Outcalt D, Ellis J, Aickin M, Valencia J, Wunsch M, and Steele L (1995) Prevalence of cardiovascular disease risk factors in a southwestern Native American tribe. Public Health Rep. *110:*742–748.
Cannon WB (1914) The emergency function of the adrenal medulla in pain and the major emotions. Am. J. Physiol. *33:*356–372.
Chester AH, Jiang C, Borland JA, Yacoub MH, and Collins P (1995) Oestrogen relaxes human epicardial coronary arteries through non-endothelium-dependent mechanisms. Coronary Artery Dis. *6:*417–422.
Chin-Hong PV and McGarvey ST (1996) Lifestyle incongruity and adult blood pressure in Western Samoa. Psychosom. Med. *58:*130–137.
Chobanian AV and Alexander RW (1996) Exacerbation of atherosclerosis by hypertension. Arch. Intern. Med. *156:*1952–1956.
Churchill D, Perry IJ, and Beevers DG (1997) Ambulatory blood pressure in pregnancy and fetal growth. Lancet *349:*7–10.
Cicinelli E, Matteo G, Ignarro LJ, Falco N, Lograno M, and Schonauer LM (1997) Acute effects of transdermal estradiol administration on plasma levels of nitric oxide in postmenopausal women. Fertil. Steril. *67:* 63–66.
Cohen MN (1989) Health and the rise of civilisation. New Haven: Yale University Press.
Davies PSW (1996) Total energy expenditure for young children. Am. J. Hum. Biol. *8:*183–188.
De Boever E, De Bacquer D, Braeckman L, Baele L, Rosseneu M, and De Backer G (1995) Relation of fibrinogen to lifestyles and to cardiovascular risk factors in a working population. Int. J. Epidemiol. *24:*915–921.
del Rio G, Velardo A, Zizzo G, Avogardo A, Cipolli C, della Casa L, Marrama P, and MacDonald IA (1994) Effect of estradiol on the sympathoadrenal response to mental stress in normal men. J. Clin. Endocrinol. Metabol. *79:*836–840.
Desai M, Crowther NJ, Ozanne SE, Lucas AE, and Hales CN (1995) Adult glucose and lipid metabolism may be programmed during fetal life. Biochem. Soc. Trans. *23:*331–335.
Dimmitt SB (1995) Recent insights into dietary fats and cardiovascular disease. Clin. Exp. Pharmacol. Physiol. *22:*204–208.
Donahoe RP, Abbott RD, Blom E, Reed DM, and Yano K (1987) Central obesity and coronary heart disease in men. Lancet *1:*821–824.
Dowse GK, Zimmet PZ, Finch CF, and Collins VR (1991) Decline in incidence of epidemic glucose intolerance in Nauruans: implications for the 'thrifty genotype.' Am. J. Epidemiol. *133:*1093–1104.
Dressler WW (1982) Hypertension and culture change: Acculturation and disease in the West Indies. New York: Redgrave.
Dressler WW (1995) Modeling biocultural interactions: Examples from studies of stress and cardiovascular disease. Yrbk. Phys. Anthropol. *38:*27–56.
Dressler WW, Dos Santos JE, and Viteri FE (1993) Social and cultural influences in the risk of cardiovascular disease in urban Brazil. In L Schell, M Smith, and A Bilsborough (eds.): Urban Ecology and Health in the Third World. Cambridge: Cambridge University Press, pp 10–25.
Dugdale AE and Lovell S (1981) The effect of early growth on distribution of subcutaneous fat in aboriginal children. Ecol. Food Nutr. *11:*53–55.
Dusting GJ (1995) Nitric oxide in cardiovascular disorders. J. Vasc. Res. *32:*143–161.
Dwyer T and Hetzel BS (1980) A comparison of trends of coronary heart disease mortality in Australia, USA and England and Wales with reference to three major risk factors—hypertension, cigarette smoking and diet. Int. J. Epidemiol. *9:*65–71.
Dyerberg J (1989) Coronary heart disease in Greenland Inuit: A paradox. Arctic Med. Res. *48:*47–54.
Edwards CRW, Benediktsson R, Lindsay RS, and Seckl JR (1993) Dysfunction of placental glucocorticoid barrier: Link between fetal environment and adult hypertension? Lancet *341:*355–357.
Elford J, Shaper AG, and Whincup P (1992) Early life experience and cardiovascular disease—ecological studies. J. Epidemiol. Community Health *46:*1–11.
Elliott P, Stamler J, Nichols R, Dyer AR, Stamler R, Kesteloot H, and Marmot M (1996) Intersalt revisited: Further analyses of 24-hour sodium excretion and blood pressure within and across populations. BMJ *312:*1249–1253.
Ellis JL and Campos-Outcalt D (1994) Cardiovascular disease risk factors in Native Americans: A literature review. Am. J. Prev. Med. *10:*295–307.
Ellison PT (1996) Age and developmental effects on human ovarian function. In L Rosetta and CGN Mascie-Taylor (eds.): Variability in Human Fertility. Cambridge: Cambridge University Press, pp 69–90.
Ellison PT, Panter-Brick C, Lipson SF, and O'Rourke MT (1993) The ecological context of human ovarian function. Hum. Reprod. *8:*2248–2258.
Elo IT and Preston SH (1992) Effects of early-life conditions on adult mortality: A review. Popul. Index *58:*186–212.
Epstein FH (1989) The relationship of lifestyle to international trends in CHD. Int. J. Epidemiol. *18:*S203–S209.
Ernst E and Resch KL (1993) Fibrinogen as a cardiovascular risk factor: A meta-analysis and review of the literature. Ann. Intern. Med. *118:*956–963.
Eveleth PB and Tanner JM (1990). Worldwide variation in human growth. Cambridge: Cambridge University Press.
Fall CHD, Barker DJP, Osmond C, Winter PD, Clark PMS, and Hales CN (1992) Relation of infant feeding to adult serum cholesterol concentration and death from ischaemic heart disease. BMJ *304:*801–805.
Farhat MY, Lavigne MC, and Ramwell PW (1996) The vascular protective effects of estrogen. FASEB J. *10:*615–624.
Feldman EB, Krisetherton P, Kritchevsky D, and Lichtenstein AH (1996) Position paper on trans-fatty acids: ASCN/AIN task force on trans-fatty acids. Am. J. Clin. Nutr. *63:*663–670.
Fontbonne A (1994) Why can high insulin levels indicate a risk for coronary heart disease? Diabetologia *37:*953–955.
Fontvieille AM, Harper IT, Ferraro RT, Sproul M, and Ravussin E (1993) Daily energy expenditure by five-year-old children, measured by doubly labelled water. J. Pediatr. *123:*200–207.
Forrester TE, Wilks RJ, Bennett FI, Simeon D, Osmond C, Allen M, Chung AP, and Scott P (1996) Fetal growth and cardiovascular risk factors in Jamaican schoolchildren. BMJ *312:*156–160.
Forsdahl A (1977) Are poor living conditions in childhood and adolescence an important risk factor for arteriosclerotic heart disease? Br. J. Prev. Soc. Med. *31:* 91–95.

Fuster V, Badimon L, Badimon JJ, and Chesebro JH (1992a) The pathogenesis of coronary artery disease and the acute coronary syndromes: Part I. New Engl. J. Med. *326:*242–250.

Fuster V, Badimon L, Badimon JJ, and Chesebro JH (1992b) The pathogenesis of coronary artery disease and the acute coronary syndromes: Part II. New Engl. J. Med. *326:*310–318.

Galanis DJ, Sobal J, McGarvey ST, Pelletier DL, and Bausserman L (1995) Ten-year changes in obesity, abdominal adiposity, and serum lipoprotein cholesterol measures of Western Samoan men. J. Clin. Epidemiol. *48:*1485–1493.

Galpin OP, Whitaker CJ, and Dubiel AJ (1992) Helicobacter pylori infection and overcrowding in childhood. Lancet *339:*619.

Garrow JS (1993) Obesity. In J Garrow and W James (eds.): Human Nutrition and Dietetics. Edinburgh: Churchill Livingstone, pp 465–479.

Goldin BR, Adlercreutz H, Gorbach SL, Woods MN, Dwyer JT, Conlon T, Bohn E, and Gershoff SN (1986) The relationship between estrogen levels and diets of Caucasian American and Oriental immigrant women. Am. J. Clin. Nutr. *44:*945–953.

Goodman KJ and Correa P (1995) The transmission of Helicobacter pylori: A critical review of the evidence. Int. J. Epidemiol. *24:*875–887.

Gracey M, Burke V, Spargo RM, Beilin LJ, Smith P, Beilby J, Smith RM, and Chin C (1996) Risk factors for ill-health in a remote desert-dwelling Aboriginal community in Western Australia. Aust. N. Z. J. Med. *26:*171–179.

Grau AJ, Buggle F, Becher H, Werle E, and Hacke W (1996) The association of leukocyte count, fibrinogen and C-reactive protein with vascular risk factors and ischemic vascular disease. Thromb. Res. *82:*245–255.

Greksa LP, Pelletier DL, and Gage TB (1986) Work in contemporary and traditional Samoa. In P Baker, J Hanna, and T Baker (eds.): The Changing Samoans: Behavior and Health in Transition. New York: Oxford University Press, pp 297–326.

Gyntelberg F, Hein HO, Suadicani P, and Sorensen H (1995) Coffee consumption and risk of ischaemic heart disease—a settled issue. J. Intern. Med. *237:*55–61.

Haffner SM and Valdez RA (1995) Endogenous sex hormones: Impact on lipids, lipoproteins, and insulin. Am. J. Med. *98* (Suppl 1A):40S–47S.

Hales CN and Barker DJP (1992) Type 2 (non-insulin-dependent) diabetes mellitus: The thrifty phenotype hypothesis. Diabetologia *35:*595–601.

Hales CN, Barker DJP, Clark PMS, Cox LJ, Fall C, Osmond C, and Winter PD (1991) Fetal and infant growth and impaired glucose tolerance at age 64. BMJ *303:*1019–1022.

Hall SM (1994) Women and drugs. In V Adesso, D Reddy, and R Fleming (eds.): Psychological Perspectives on Women's Health. Washington, DC: Taylor and Francis, pp 101–126.

Heller RF and Heller RF (1995) Profactor H (elevated circulating insulin)—the link to health. Med. Hypotheses *45:*325–330.

Hodge AM, Dowse GK, Erasmus RT, Spark RA, Nathaniel K, Zimmet PZ, and Alpers MP (1996a) Serum lipids and modernization in coastal and highland Papua New Guinea. Am. J. Epidemiol. *144:*1129–1142.

Howard BV, Lee ET, Cowan LD, Fabsitz RR, Howard WJ, Oopik AJ, Robbins DC, Savage PJ, Yeh JL, and Welty TK (1995) Coronary heart disease prevalence and its relation to risk factors in American Indians: The Strong Heart Study. Am. J. Epidemiol. *142:*254–268.

Hunter E (1993) Aboriginal health and history: Power and prejudice in remote Australia. Cambridge: Cambridge University Press.

James GD, Jenner DA, Harrison GA, and Baker PT (1985) Differences in catecholamine excretion rates, blood pressure and lifestyle among young Western Samoan men. Hum. Biol. *57:*635–647.

James GD, Crews DE, and Pearson J (1989) Catecholamines and stress. In M Little and J Haas (eds.): Human Population Biology. Oxford: Oxford University Press, pp 280–295.

James SA (1987) Psychosocial precursors of hypertension: A review of the epidemiologic evidence. Circulation *76* (Suppl 1)*:*I60–I66.

James WTP (1993) Diseases of the heart and circulation: the role of dietary factors in aetiology and management. In J Garrow and W James (eds.): Human Nutrition and Dietetics. Edinburgh: Churchill Livingstone, pp 619–650.

Janes CR (1990) Migration, changing gender roles and stress: The Samoan case. Med. Anthropol. *12:*145–167.

Jarrett RJ (1994) Why is insulin not a risk factor for coronary heart disease? Diabetologia *37:*945–947.

Jenkins CD (1988) Epidemiology of cardiovascular diseases. J. Consult. Clin. Psychol. *56:*324–332.

Jenner DA, Harrison GA, and Prior IAM (1987) Catecholamine excretion in Tokelauans living in three different environments. Hum. Biol. *59:*165–172.

Johansson G and Lundberg U (1978) Psychophysiological aspects of stress and adaptation in technological societies. In V Reynolds and N Blurton Jones (eds.): Human Behaviour and Adaptation. London: Taylor and Francis, pp 285–303.

Julian DG and Cowan JC (1992) Cardiology. London: Bailliere Tindall.

Kannel WB (1987) New perspectives on cardiovascular risk factors. Am. Heart J. *114:*213–219.

Karas RH, Patterson BL, and Mendelsohn ME (1994) Human vascular smooth muscle cells contain functional estrogen receptor. Circulation *89:*1943–1950.

Karasek R and Theorell T (1990) Healthy work: Stress, productivity, and the reconstruction of working life. New York: Basic.

Karvonen M, Tuomilehto J, Pitkaniemi J, Naukkarinen A, and Saikku P (1994) Importance of smoking for *Chlamydia pneumoniae* seropositivity. Int. J. Epidemiol. *23:*1315–1321.

Key TJA, Chen J, Wang DY, Pike MC, and Boreham J (1990) Sex hormones in women in rural China and in Britain. Br. J. Cancer *62:*631–636.

Keys A, Menotti A, Karvonen MJ, Aravanis C, Blackburn H, Buzina R, Djordjevic BS, Dontas AS, Fidanza F, Keys MH, Kromhout D, Nedeljkovic S, Punsar S, Seccareccia F, and Toshima H (1986) The diet and 15-year death rate in the Seven Countries Study. Am. J. Epidemiol. *124:*903–915.

Kharatinov SA, Logan-Sinclair RB, Busset CM, and Shinebourne EA (1994) Peak expiratory nitric oxide differences in men and women: Relation to the menstrual cycle. Br. Heart J. *72:*243–245.

Kirk RL (1981) Aboriginal Man Adapting: The Human Biology of Australian Aborigines. Oxford: Oxford University Press.

Knopp RH, Zhu X, and Bonet B (1994) Effects of estrogens on lipoprotein metabolism and cardiovascular disease in women. Atherosclerosis *110*(Suppl):S83–S91.

Konner M and Worthman C (1980) Nursing frequency, gonadal function, and birth spacing among the !Kung hunter-gatherers. Science *207:*788–791.

Koupilova I, Leon DA, and Vagero D (1997) Can confounding by sociodemographic and behavioural fac-

tors explain the association between size at birth and blood pressure at age 50 in Sweden. J. Epidemiol. Community Health *51:*14–18.
Kramer MS and Joseph KS (1996) Enigma of fetal/infant-origins hypothesis. Lancet *348:*1254–1255.
Krantz DS, Contrada RJ, Hill R, and Friedler E (1988) Environmental stress and biobehavioral antecedents of coronary heart disease. J. Consult. Clin. Psychol. *56:*333–341.
Kuh D and Smith GD (1993) When is mortality risk determined? Historical insights into a current debate. Soc. Hist. Med. *6:*101–123.
Kuller LH, Tracy RP, Shaten J, and Meilahn EN (1996) Relation of C-reactive protein and coronary heart disease in the MRFIT nested case-control study. Am. J. Epidemiol. *144:*537–547.
Kunitz SJ (1990) Public policy and mortality among indigenous populations of Northern America and Australasia. Popul. Dev. Rev. *16:*647–672.
Kunitz SJ (1994) Disease and social diversity: The European impact on the health of non-Europeans. New York: Oxford University Press.
Kuo PC and Schroeder RA (1995) The emerging multifaceted roles of nitric oxide. Ann. Surg. *221:*220–235.
Lapidus L, Bengtsson C, Larsson B, Pennert K, Rybo E, and Sjostrom L (1984) Distribution of adipose tissue and risk of cardiovascular disease and death: A 12-year follow-up of participants in the population study of women in Gothenburg, Sweden. BMJ *289:*1257–1261.
Law CM and Barker DJP (1994) Fetal influences on blood pressure. J. Hypertens. *12:*1329–1332.
Law CM and Shiell AW (1996) Is blood pressure inversely related to birth weight? The strength of the evidence from a systematic review of the literature. J. Hypertens. *14:*935–941.
Law CM, Barker DJP, Osmond C, Fall CHD, and Simmonds SJ (1992) Early growth and abdominal fatness in adult life. J. Epidemiol. Community Health *46:*184–186.
Leon DA, Koupilova I, Lithell HO, Berglund L, Mohsen R, Vagero D, Lithell UB, and McKeigue PM (1996) Failure to realise growth potential in utero and adult obesity in relation to blood pressure in 50 year old Swedish men. BMJ *312:*401–406.
Lindheim SR, Legro RS, Bernstein L, Stanczyk FZ, Vijod MA, Presser SC, and Lobo RA (1992) Behavioral stress responses in premenopausal and postmenopausal women and the effects of estrogen. Am. J. Obstet. Gynecol. *167:*1831–1836.
Linnanmaki E, Leinonen M, Mattila K, Nieminen MS, Valtonen V, and Saikku P (1993) Chlamydia pneumoniae-specific circulating immune complexes in patients with chronic coronary heart disease. Circulation *87:*1130–1134.
Lithell HO, McKeigue PM, Berglund L, Mohsen R, Lithell UB, and Leon DA (1996) Relation of size at birth to non-insulin dependent diabetes and insulin concentrations in men aged 50–60 years. BMJ *312:* 406–410.
Lloyd BL (1994) Declining cardiovascular disease incidence and environmental components. Aust. N. Z. J. Med. *24:*124–132.
Lopes-Virella MF and Virella G (1985) Immunological and microbiological factors in the pathogenesis of atherosclerosis. Clin. Immunol. Immunopathol. *37:* 377–386.
Lopez AD (1993) Assessing the burden of mortality from cardiovascular diseases. World Health Stat. Q. *46:* 91–96.
Lowenstein CJ, Dinerman JL, and Snyder SH (1994) Nitric oxide: A physiologic messenger. Ann. Intern. Med. *120:*227–237.
Lüscher TF and Noll G (1995) The pathogenesis of cardiovascular disease: Role of the endothelium as a target and mediator. Atherosclerosis *118* (Suppl):S81–S90.
Luzza F, Maletta M, Imeneo M, Marcheggiano A, Iannoni C, Biancone BSL, and Pallone F (1995) Salivary-specific immunoglobulin G in the diagnosis of Helicobacter pylori infection in dyspeptic patients. Am. J. Gastroenterol. *90:*1820–1823.
Mackenzie HS and Brenner BM (1995) Fewer nephrons at birth: A missing link in the etiology of essential hypertension? Am. J. Kidney Dis. *26:*91–98.
Marmot MG (1984) Alcohol and coronary heart disease. Int. J. Epidemiol. *13:*160–167.
Martyn CN, Barker DJP, Jesperson S, Greenwald S, Osmond C, and Berry C (1995) Growth in utero, adult blood pressure, and arterial compliance. Br. Heart J. *73:*116–121.
Martyn CN, Barker DJP, and Osmond C (1996) Mothers' pelvic size, fetal growth, and death from stroke and coronary heart disease in men in the UK. Lancet *348:*1264–1268.
Matthews KA (1989) Interactive effects of behavior and reproductive hormones on sex differences in risk for coronary heart disease. Health Psychol. *8:*373–387.
McCance DR, Pettitt DJ, Hanson RL, Jacobsson LTH, Knowler WC, and Bennett PH (1994) Birth weight and non-insulin dependent diabetes: thrifty genotype, thrifty phenotype, or surviving small baby genotype? BMJ *308:*942–945.
McCann BS, Magee MS, Broyles FC, Vaughan M, Albers JJ, and Knopp RH (1995) Acute psychological stress and epinephrine infusion in normolipidemic and hyperlipidemic men: Effects of plasma lipid and apoprotein concentrations. Psychosom. Med. *57:*165–176.
McGarvey ST (1994) The thrifty gene concept and adiposity studies in biological anthropology. J. Polynes. Soc. *103:*29–42.
McGarvey ST, Bindon JR, Crews DE, and Schendel DE (1989) Modernization and adiposity: causes and consequences. In M Little and J Haas (eds.): Human Population Biology. Oxford: Oxford University Press, pp 263–280.
Melby CL, Toohey ML, and Cebrik I (1994) Blood pressure and blood lipids among vegetarian, semivegetarian, and nonvegetarian African-Americans. Am. J. Clin. Nutr. *59:*103–109.
Mendall MA, Goggin PM, Molineaux N, Levy J, Toosy T, Strachan D, and Northfield TC (1992) Childhood living conditions and Helicobacter pylori seropositivity in adult life. Lancet *339:*896–897.
Mendall MA, Goggin PM, Molineaux N, Levy J, Toosy T, Strachan D, Camm AJ, and Northfield TC (1994) Relation of Helicobacter pylori infection and coronary heart disease. Br. Heart J. *71:*437–439.
Mendall MA, Patel P, Ballam L, Strachan D, and Northfield TC (1996) C reactive protein and its relation to cardiovascular risk factors: a population based cross sectional study. BMJ *312:*1061–1065.
Meneely GR and Battarbee HD (1976) High sodium-low potassium environment and hypertension. Am. J. Cardiol. *38:*768–784.
Mitchell HM, Li YY, Hu PJ, Liu Q, Chen M, Du GG, Wang ZJ, Lee A, and Hazell SL (1992) Epidemiology of Helicobacter pylori in Southern China: Identification of early childhood as the critical period for acquisition. J. Infect. Dis. *166:*149–153.
Morris MC, Sacks F, and Rosner B (1993) Does fish oil lower blood pressure: A meta-analysis of controlled trials. Circulation *88:*523–533.
Murray LJ, Bamford KB, O'Reilly DPJ, McCrum EE, and Evans AE (1995) Helicobacter pylori infection: relation with cardiovascular risk factors, ischaemic

heart disease, and social class. Br. Heart. J. *74:*497–501.
Muscat JE, Harris RE, Haley NJ, and Wynder EL (1991) Cigarette smoking and plasma cholesterol. Am. Heart. J. *121:*141–147.
Neel JV (1962) Diabetes mellitus: a 'thrifty' genotype rendered detrimental by 'progress'? Am. J. Hum. Genet. *14:*353–362.
Niemelä S, Karttunen T, Korhonen T, Laara E, Karttunen R, Ikaheimo M, and Kesaniemi YA (1996) Could Helicobacter pylori infection increase the risk of coronary heart disease by modifying serum lipid concentrations? Heart *75:*573–575.
O'Dea K (1984) Marked improvement in carbohydrate and lipid metabolism in diabetic Australian Aborigines after temporary reversion to traditional lifestyle. Diabetologia *22:*148–153.
Osmond C, Barker DJP, Winter PD, Fall CHD, and Simmonds SJ (1993) Early growth and death from cardiovascular disease in women. BMJ *307:*1519–1524.
Patel P, Carrington D, Strachan DP, Leatham E, Goggin P, Northfield TC, and Mendall MA (1994) Fibrinogen: A link between chronic infection and coronary heart disease. Lancet *343:*1634–1635.
Patel P, Mendall MA, Carrington D, Strachan DP, Leatham E, Molineaux N, Levy J, Blakeston C, Seymour CA, Camm AJ, and Northfield TC (1995) Association of Helicobacter pylori and Chlamydia pneumoniae infections with coronary heart disease and cardiovascular risk factors. BMJ *311:*711–714.
Pauletto P, Puato M, Caroli MG, Casiglia E, Munhambo AE, Cazzolato G, Bon GB, Angeli MT, Galli C, and Pessina AC (1996) Blood pressure and atherogenic lipoprotein profiles of fish-diet and vegetarian villagers in Tanzania: The Lugalawa study. Lancet *348:*784–788.
Pearson TA, Jamison DT, and Trejo-Gutierrez J (1993) Cardiovascular disease. In D Jamison, W Mosley, A Measham, and J Bobadilla (eds.): Disease Control Priorities in Developing Countries. New York: Oxford University Press, pp 577–594.
Petrie JR, Ueda S, Webb DJ, Elliott HL, and Connell JMC (1996) Endothelial nitric oxide production and insulin sensitivity. Circulation *93:*1331–1333.
Phillips DIW, Barker DJP, Hales CN, Hirst S, and Osmond C (1994) Thinness at birth and insulin resistance in adult life. Diabetologia *37:*150–154.
Pollard TM (1995) Use of cortisol as a stress marker: Practical and theoretical problems. Am. J. Hum. Biol. *7:*265–274.
Pollard TM, Brush G, and Harrison GA (1991) Geographic distribution of within-population variability in blood pressure. Hum. Biol. *63:*643–661.
Preuss HG, Gondal JA, and Lieberman S (1996) Association of macronutrients and energy intake with hypertension. J. Am. Coll. Nutr. *15:*21–35.
Rathbone B, Martin D, Stephens J, Thompson JR, and Samani NJ (1996) Helicobacter pylori seropositivity in subjects with acute myocardial infarction. Heart *76:*308–311.
Reaven GM (1988) Role of insulin resistance in human disease. Diabetes *37:*1595–1607.
Reaven GM and Laws A (1994) Insulin resistance, compensatory hyperinsulinaemia, and coronary heart disease. Diabetologia *37:*948–952.
Replogle ML, Glaser SL, Hiatt RA, and Parsonnet J (1995) Biologic sex as as risk factor for Helicobacter pylori in healthy young adults. Am. J. Epidemiol. *142:*856–863.
Report of the Cardiovascular Review Group Committee on Medical Aspects of Food Policy (1994) Nutritional aspects of cardiovascular disease. London: HMSO.
Rona RJ, Qureshi S, and Chinn S (1996) Factors related to total cholesterol and blood pressure in British 9 year olds. J. Epidemiol. Community Health *50:*512–518.
Rosselli M, Imthurn B, Keller PJ, Jackson EK, and Dubey RK (1995) Circulating nitric oxide (nitrite/nitrate) levels in postmenopausal women substituted with 17β-estradiol and norethisterone acetate. Hypertension *25:*848–853.
Saab PG, Matthews KA, Stoney CM, and McDonald RH (1989) Premenopausal and postmenopausal women differ in their cardiovascular and neuroendocrine responses to behavioral stressors. Psychophysiology *26:*270–280.
Saikku P, Leinonen M, Mattila K, Ekman MR, Nieminen MS, Makela PH, Huttunen JK, and Valtonen V (1988) Serological evidence of an association of a novel Chlamydia, TWAR, with chronic coronary heart disease and acute myocardial infarction. Lancet. *ii:*983–986.
Saikku P, Leinonen M, Tenkanen L, Linnanmaki E, Ekman MR, Manninen V, Manttari M, Frick MH, and Huttenen JK (1992) Chronic Chlamydia pneumoniae infection as a risk factor for coronary heart disease in the Helsinki heart study. Ann. Intern. Med. *116:*273–278.
Schall JI (1995) Sex differences in the response of blood pressure to modernization. Am. J. Hum. Biol. *7:*159–172.
Scragg R, Baker J, Metcalf P, and Dryson E (1993) Serum lipid levels in a New Zealand multicultural workforce. N. Z. Med. J. *106:*96–99.
Scragg RKR, Fraser A, and Metcalf PA (1996) Helicobacter pylori seropositivity and cardiovascular risk factors in a multicultural workforce. J. Epidemiol. Community Health *50:*578–579.
Seidell JC (1995) Obesity in Europe: Scaling an epidemic. Int. J. Obesity *19* (Suppl 3)*:*S1–S4.
Selye H (1956) The stress of life. New York: McGraw Hill.
Shaper AG (1995) Alcohol and coronary heart disease. Eur. Heart J. *16:*1760–1764.
Shephard RJ and Rode A (1996) The health consequences of 'modernization': Evidence from the circumpolar peoples. Cambridge: Cambridge University Press.
Shively CA, Knox SS, Sherwin BB, Walsh BW, and Wilson PWF (1993) Sex steroids, psychosocial factors, and lipid metabolism. Metabolism *42* (Suppl 1)*:*16–24.
Smith RM, Spargo RM, King RA, Hunter EM, Correll RL, and Nestel PJ (1992) Risk factors for hypertension in Kimberley Aborigines. Med. J. Aust. *156:*562–566.
Sorlie PD, Adam E, Melnick SL, Folsom A, Skelton T, Chambless LE, Barnes R, and Melnick JL (1994) Cytomegalovirus herpesvirus and carotid atherosclerosis: The ARIC Study. J. Med. Virol. *42:*33–37.
Stampfer MJ and Colditz GA (1991) Estrogen replacement therapy and coronary heart disease: A quantitative assessment of the epidemiologic evidence. Prev. Med. *20:*47–63.
Stampfer MJ and Rimm EB (1995) Epidemiologic evidence for vitamin E in prevention of cardiovascular disease. Am. J. Clin. Nutr. *62:*S1365–S1369.
Steel DM and Whitehead AS (1994) The major acute phase reactants: C-reactive protein, serum amyloid P component and serum amyloid A protein. Immunol. Today *15:*81–88.
Stein CE, Fall CHD, Kumaran K, Osmond C, Cox V, and Barker DJP (1996) Fetal growth and coronary heart disease in South India. Lancet *348:*1269–1273.

Stern MP (1994) The insulin resistance syndrome: The controversy is dead, long live the controversy! Diabetologia *37:*956–958.

Stern MP (1996) Do non-insulin-dependent diabetes mellitus and cardiovascular disease share common antecedents? Ann. Intern. Med. *124:*110–116.

Sung JJY and Sanderson JE (1996) Hyperhomocysteinaemia, Helicobacter pylori, and coronary heart disease. Heart *76:*305–307.

Thom DH, Grayston JT, Siscovick DS, Wang SP, Weiss NS, and Daling JR (1992) Association of prior infection with Chlamydia pneumoniae and angiographically demonstrated coronary artery disease. JAMA *268:*68–72.

Toren C (1994) The drinker as chief or rebel: Kava and alcohol in Fiji. In M McDonald (ed.): Gender, Drink and Drugs. Oxford: Berg, pp 153–174.

Trowell HC and Burkitt DP (1981) Western diseases: their emergence and prevention. Cambridge, MA: Harvard University Press.

Uemura K and Pisa Z (1988) Trends in cardiovascular disease mortality in industrialized countries since 1950. World Health Stat. Q. *41:*155–178.

Ulijaszek SJ (1995) Human energetics in biological anthropology. Cambridge: Cambridge University Press.

Ulijaszek SJ (1996) Energetics, adaptation and adaptability. Am. J. Hum. Biol. *8:*169–182.

Valdez R, Athens MA, Thompson GH, Bradshaw BS, and Stern MP (1994) Birth weight and adult health outcomes in a biethnic population in the USA. Diabetologia *37:*624–631.

Van Poppel G, Kardinaal A, Princen H, and Kok FJ (1994) Antioxidants and coronary heart disease. Ann. Med. *26:*429–434.

Wannamethee SG, Whincup PH, Shaper G, and Walker M (1996) Influence of fathers' social class on cardiovascular disease in middle-aged men. Lancet *348:*1259–1263.

Webb PM, Knight T, Greaves S, Wilson A, Newell DG, Elder J, and Forman D (1994) Relation between infection with Helicobacter pylori and living conditions in childhood: Evidence for person to person transmission in early life. BMJ *308:*750–753.

Weder AB and Schork NJ (1994) Adaptation, allometry, and hypertension. Hypertension *24:*145–156.

Whincup P, Cook D, Papacosta O, and Walker M (1995) Birth weight and blood pressure: Cross sectional and longitudinal relations in childhood. BMJ *311:*773–776.

Whincup PH, Mendall MA, Perry IJ, Strachan DP, and Walker M (1996) Prospective relations between Helicobacter pylori infection, coronary heart disease, and stroke in middle aged men. Heart *75:*568–572.

Worthman CM (1995) Hormones, sex, and gender. Ann. Rev. Anthropol. *24:*593–616.

Yarnell JWG, Baker IA, Sweetnam PM, Bainton D, O'Brien JR, Whitehead PJ, and Elwood PC (1991) Fibrinogen, viscosity, and white blood cell count are major risk factors for ischemic heart disease: The Caerphilly and Speedwell collaborative heart disease studies. Circulation *83:*836–844.

Young DB, Lin H, and McCabe RD (1995) Potassium's cardiovascular protective mechanisms. Am. J. Physiol. *37:*R825–R837.

Zimmet P, Taft P, and Guinea A (1977) The high prevalence of diabetes mellitus on a central Pacific island. Diabetologia *13:*111–115.